REMARKS

This amendment is submitted in an earnest effort to bring this case to issue without delay.

Applicants wish to reiterate their claim to the benefit of their Turkish Priority Date of 18 April 2003 pursuant to 35 USC 119, 37 CFR 1.55 and the International Convention. A certified copy of Turkish Patent Application TR 2003/510 filed 18 April 2003 accompanies this amendment. Applicants wish to make it clear that it is not too late for them to perfect their right to the benefit of their Turkish Priority date since Applicants timely made their claim to the benefit of their Turkish priority date at the time they filed the present application, namely, 14 April 2004. Applicants have the right to submit the certified copy of their priority document at any time before the issue fee is paid without taking any additional steps, and even after that date by filing a petition. See 37 CFR 1.55. Now that Applicant has made of record the certified copy of their Turkish priority document, the Examiner is respectfully requested to acknowledge the Applicants' perfected right of priority.

Applicants have amended the specification on pages 3 and 5 to make it clear that PROTANAL® LFR 5/60, MUNUCOL® LB, and EUDRAGIT® E100 are all registered trademarks. All three marks appear now in capital letters and include the symbol of an R within

a circle to show that the marks are registered trademarks. In the case of PROTANAL® LFR 5/60, MUNUCOL® LB the generic terminology is already indicated in the specification that the marks stand for alginic acid or sodium alginate. In the case of EUDRAGIT® E100, Applicants have amended the specification to indicate that EUDRAGIT® E100 is poly(butyl methacrylate, 2-dimethylaminoethyl methacrylate, and methyl methacrylate) in a ratio of 1:2:1. Applicants include a printout from the literature providing further details of this coating that is well known in the pharmaceutical industry.

Applicants have amended claim 1 to remove the periods following the letters a, b and c, to which the Examiner has objected.

Applicants have amended claims 4 and 8 to delete reference to "derivatives", which the Examiner contends is beyond the scope of the level of enablement provided by the disclosure in the specification. Thus Applicants have now removed any basis to reject any claim now presented under 35 USC 112, first paragraph, on the grounds of lack of enablement.

Applicants have amended claims 3 through 6 to delete any reference to expressions beginning with "preferably" or ending with "is preferred". Thus there are no longer any improper alternative expressions within the claims and so no rejection of any now presented should be rejected under 35 USC 112, second paragraph, as in definite for use of such improper alternative expressions.

Applicants have amended claims 1 and 10, to make it clear that the alginic acid, sodium alginate or mixtures thereof are employed in the presently claimed invention in an amount therapeutically effective to prevent esophageal reflux, heartburn and esophagitis in a patient taking alendronate. Antecedent basis for this expression may be found in the specification on page 1, lines 15 to 18. Furthermore Applicants have amended claims 1 and 10 to make it clear that these pharmaceutical formulations are packaged into a sachet and then orally administered. Antecedent basis may be found in the specification on page 3, lines 13 through 17. Thus claims 1 through 10 remain the application and are again presented for examination. The sachet is dispersed into a glass of water, preferably holding about 250 ml, and is administered orally to the patient.

Now Applicants turn to the rejection of all claims in view of the prior art as obvious under 35 USC 103. The Examiner has combined WO 03/003999 A2 to CLANCY et al together with US Patent 6,248,363 to PATEL et al to contend that all claims as last presented are directed to obvious subject matter that is unpatentable according to 35 USC 103. Applicants believe that no rejection of any claim now presented should be maintained under 35 USC 103 in view of CLANCY et al, PATEL or a combination of CLANCY et al and PATEL et al. Applicants are the first to prepare pharmaceutical compositions in the form of sachets that contain alendronate, coated with a polymer such as EUDRAGIT® E 100

(polybutyl methacrylate/(2-dimethylaminoethyl) methacrylate/ methyl methacrylate) in a 1:2:1 ratio and a therapeutically effective amount of alginic acid, sodium alginate or a mixture thereof to protect the patient taking alendronate from esophageal reflux, heartburn and esophagitis. Neither CLANCY et al nor PATEL et al, nor the combination thereof, discloses nor suggests such a composition. For these reasons alone Applicants strongly believe that neither of the cited references taken individually, or in combination suggests the presently claimed invention.

Applicants now have the following direct comments in response to the Examiner's rejection of the claims last presented as obvious in view of the combination of CLANCY et al and PATEL et al:

First Applicants want to mention, the presently claimed sachet formulation comprises alendronate microparticles coated with EUDRAGIT® E 100 which is insoluble at pH 6-7.5, and which further comprises a therapeutically effective amount of sodium alginate or alginic acid in order to eliminate the side effects of alendronate that arise in the esophagus and stomach. Note that the Example on page 5 of the specification shows 10 mg of alendronic acid and 300 mg of sodium alginate There is no disclosure or suggestion of such sachet formulations in either of the documents.

The CLANCY et al reference does not destroy the novelty or the inventiveness of the presently claimed invention since the

problem that CLANCY et al seeks to overcome is a totally different problem. In CLANCY et al the problem is the low bioavailability of alendronate since it is absorbed poorly in the gastrointestinal tract of the individual patient. As a solution to this problem, *CLANCY* offered encapsulation of alendronate with polyoxyethylene/polyoxypropylene copolymer. The point of encapsulating alendronate in the presently claimed invention is for a totally different reason which is the elimination of any irritation related to alendronate sodium during its passage through the esophagus by ensuring that it is released neither in the mouth nor in the esophagus. Therefore Applicants are using copolymers which are specific for the solution of this problem. The copolymers used are pH dependent so that they are insoluble at pH 6-7.5.

In the office action, it is pointed out that additional excipients are used in both CLANCY et al compositions and in Applicants' formulation. The aim of the Applicants' presently claimed invention is to prevent the side effects of alendronate sodium on the patient's esophagus and stomach but not merely by using excipients. And in order to solve this problem Applicants use a coating and add a therapeutically effective amount of alginate or alginic acid to the formulation, which according to the Example on page 5 of the specification is 30 times the amount of the alendronate. Additionally, other excipients have to be included in a formulation as all pharmaceutical formulations.

It is also mentioned in the office action that CLANCY et al teaches the use of enteric coatings and that the reference encloses a list of examples to enteric coatings including EUDRAGIT®. First of all, in Applicants' presently claimed invention, the purpose of including the EUDRAGIT® 100 as a coating on the alendronate is to ensure that the alendronate does not degrade in the esophagus or in the mouth. In other words Applicants are taking advantage of the pH-dependent solubility of the copolymer. But in CLANCY et al they teach enteric coatings which are designed to degrade or dissolve in the intestinal tract but not in the stomach. And also the formulations themselves that Applicants presently claim are different from those of the reference. The CLANCY et al compositions are either capsules or tablets as a subject of the invention. See e.g. page 23 lines 8 - 14. But Applicants' alendronate is in sachet form. So CLANCY et al is using EUDRAGIT® polymers to coat the whole capsule or the tablet which then contains alendronate. But in Applicants' case, they coat the active ingredient, alendronate, itself, and not the outside of a capsule containing the active ingredient.

Also, as mentioned in the office action, CLANCY et al does not disclose or teach the use of sodium alginate, saccharine salts, microcrystalline cellulose and EUDRAGIT® E 100, either as a mere excipient or as a therapeutically active ingredient as in the presently claimed compositions.

Nor does combining CLANCY et al with PATEL et all provide any basis to reject any claim now presented as obvious to provide pharmaceutical compositions in the form of sachets for improved delivery of a wide variety of pharmaceutically active ingredients. (See e.g. abstract, first sentence; and also the "field of invention in column 1) And also, in the description part of this patent, almost all possible active ingredients, all possible excipients, surfactants, triglycerides, substrates, diluents, sweeteners, processes, all possible specific formulations and methods are listed. It seems more like a summary; therefore it is almost impossible not to have anything in common with this document. Applicants' invention is much more specific, Applicants are suggesting a specific solution for a particular problem of alendronate sodium.

It is pointed out that in PATEL et al, alendronate sodium and sodium alginate appear in the same formulation in Example 14. In the presently claimed invention, Applicants use alendronate sodium and sodium alginate in the same formulation but there is one significant difference between the compositions disclosed in PATEL et al and those presently claimed. In Applicants' presently claimed invention, alginic acid or sodium alginate is used in therapeutically effective amounts. The point of using this agent is to use an amount that is effective to protect the patient who is taking alendronate sodium as a bone resorption inhibitor from esophageal reflux. In the example on page 5 of the application,

Applicants use 30 times the amount of alginic acid with respect to the amount of alendronate. Example 14 of PATEL uses 50 parts of alendronate sodium and 2 grams of sodium alginate, a minuscule amount of the sodium alginate, far removed from the amounts the Applicants employ. Alginic acid and/or sodium alginates are used for their protective effect in the gastrointestinal tract in the present invention in therapeutically effective amounts to prevent esophageal reflux, heartburn and esophagitis in a patient taking alendronate. And another point is, the alendronate sodium used in the formulation given in the Example 14 of PATEL et al is not coated with a polymer. Only in Applicants' presently claimed pharmaceutical formulations, is the alendronate sodium coated with a polymer, then mixed with alginates in a therapeutically effective amount as explained hereinabove, and placed in a sachet.

The Examiner points out that similar sweeteners are used in Applicants' invention referring to col. 40 lines 53-56 and col. 30 lines 45-59 of PATEL et al. And it is also pointed out that in both documents, diluents and flavorants are used. As mentioned before, in PATEL et al almost all possible sweeteners and additives such as diluents and flavorants are listed in the description part. Microcrystalline cellulose and EUDRAGIT® E100 are also mentioned in both documents, but microcrystalline cellulose appears under the "substrate" classification in PATEL et al whereas Applicants use it as a diluent in the present invention. And similarly, EUDRAGIT® E100 is taught as a taste masking agent although the point of using

this polymer is to coat the active material in the present invention so that it will not dissolve in the mouth or esophagus. In other words Applicants took advantage of the insolubility of EUDRAGIT® E100 at a pH range of 6 to 7.5.

Applicants again emphasize that the formulations disclosed in CLANCY et al are directed to alendronate sodium coated with polyoxyethylene/polyoxypropylene block copolymer for improving the bioavailability of alendronate in the small intestines. But in Applicants' case, they use poly(butyl methacrylate, (2-dimethyl aminoethyl) methacrylate, methyl methacrylate) 1:2:1 copolymer to coat the active ingredient and mix the coated active ingredient with a therapeutically effective amount of alginic acid or sodium alginate for a completely different reason which is to overcome the problems associated with the side effects of alendronate on the esophagus. It has to be clear to the person skilled in the art that although both formulations contain a copolymer, the copolymers are different and the utilization of each is different. And also as mentioned in the text, PATEL et al teaches the utilization of sodium alginate merely as an excipient whereas in Applicants' invention sodium alginate is being used in therapeutic amounts for its protective effects in the gastrointestinal tract. EUDRAGIT® E100 (poly(butyl methacrylate, (2-dimethyl aminoethyl) methacrylate, methyl methacrylate) 1:2:1 copolymer) is not for taste improvement or bioavailability enhancement purposes as in the

case of PATEL et al; but it is used as a coating agent as mentioned before in the text.

As a result, Applicants conclude that neither CLANCY et al nor PATEL et al or the combination thereof can motivate one skilled in the art to arrive at the presently claimed invention. Because the starting point for this invention is to find a specific solution to a specific problem and it is completely different from the disclosures in both references, that is to eliminate the side effects of the corresponding active agent, alendronate sodium, on the esophagus and the stomach. Thus no rejection of any claim now presented as obvious should be maintained under 35 USC 103 in view of CLANCY et al and PATEL et al.

Applicants are enclosing a copy of an International Search Report in English carried out by the European Patent Office in the corresponding PCT/TR2004/000024 filed 19 April 2004 and published on 11 November 2004. Applicants have listed all cited references or an equivalent US Patent or US Patent Publication on Form PTO 1449 attached hereto. Applicants are also enclosing a copy of WO03/043641, cited in the International Search Report, which has no US equivalent. Applicants are also enclosing PTO Form 2038 authorizing the US Patent and Trademark Office to charge to the credit card of the undersigned attorneys the fee for considering the prior art cited in the International Search Report.

Applicants believe that all claims now presented are in condition for allowance and a response to that effect is earnestly solicited.

Respectfully submitted,
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Enclosures:
Transmittal of Priority Papers Form with
Certified Copy of Turkish Priority Document

Internet Excerpt Describing EUDRAGIT® E100

International Search Report carried out by EPO in the European Phase of the corresponding International patent Application

Patent Application Statement from EPO of Intent to grant a European Patent in the European Phase of the Corresponding International Patent Application

PTO 1449 with WO03/043641
PTO 2038 (PRIOR ART )
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